Hepatocellular carcinoma: management of an increasingly common problem

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Hepatocellular carcinoma (HCC) is a common cancer that typically occurs in the setting of cirrhosis and chronic hepatitis virus infections. Hepatitis B and C account for approximately 80% of cases worldwide. HCC is currently the fifth most common malignancy in men and the eighth in women worldwide; its incidence is increasing dramatically in many parts of the world. Recognition of those at risk and early diagnosis by surveillance with imaging, with or without serologic testing, are extremely important. Many highly effective and even curative therapies are now available and include resection, liver transplantation, and local ablation. Appropriate application of these interventions offers hope of prolonged survival to many patients with this otherwise lethal complication of liver disease.

Hepatocellular carcinoma (HCC) is a primary cancer of hepatocytes (liver cells) that most typically occurs in the setting of known risk factors including, among others, cirrhosis and chronic hepatitis virus infections. Hepatitis B and C account for approximately 80% of cases worldwide. Accordingly, the incidence of HCC has both geographic and time-dependent variation related to the prevalence of viral hepatitis in the population over recent decades. HCC was the fifth most common malignancy in men and the eighth in women worldwide in 2000. The recent availability of effective therapies for HCC, including local ablation, chemoembolization, radioembolization, and transplantation, make early identification more important.

EPIDEMIOLOGY

According to the World Health Organization, cancer is a leading cause of death worldwide, accounting for 13% of all deaths. Liver cancer accounts for 662,000 deaths and is the third leading cause of cancer-related death, exceeded only by cancer of the lung and stomach (1). Liver cancer is more common than cancer of the colon or breast. There is considerable geographic variability in the estimated number of cases and the age-adjusted incidence of HCC. (Note: Age-adjusted incidence rates represent averages per 100,000 using the world population as a standard. Accordingly, the rate is adjusted upward in countries where the average age is low and artificially lowered in countries where the average age is higher; this provides a useful method to more accurately compare average rates between countries.) Approximately 75% to 80% of cases of HCC occur in Asia (1, 2). However, there is considerable variation within continents. The rate in Mongolia, for example, is 98.9 per 10^5; in Korea, 48.8 per 10^5; in Japan, 29.2 per 10^5; and in mainland China, in the mid-30 range (2). Similarly, the rates in southern and middle Africa are lower (Angola, 5.8 per 10^5) than in western Africa (Congo, 23.3 per 10^5; Cameroon, 17.7 per 10^5; Guinea, 33.2 per 10^5). The rates in these countries are tied to the prevalence of risk factors, particularly hepatitis B, that are discussed later.

In the USA, HCC is much less common than in other parts of the world and accounts for only about 16,000 or 2.9% of cancer deaths (3). The cumulative lifetime risk of liver cancer (data include both HCC and bile duct cancer, although HCC accounts for approximately 85% of cases) is only 0.88% in men and 0.42% in women; the risk relative to the overall population is 0.84/0.85 (male/female) in whites, 1.04/0.90 in blacks, 1.18/1.90 in Hispanics, and 2.80/2.98 in Asians–Pacific Islanders (4). These data undoubtedly underestimate the true risk of malignancy since they rely upon proper coding and reporting and confirmation of malignancy (usually requiring histology, particularly before 1990). Nonetheless, they provide general estimates of population risk. The differences between racial groups reflect the prevalence of viral hepatitis in those populations. Interestingly, the high risk in Asian immigrants decreases in successive generations. King reported that the lifetime risk of dying from HCC decreased from 10.9 per 10^5 in the first generation of male immigrants to 2.8 in the second generation (5). Others have confirmed these observations (6).

The age-adjusted incidence of HCC is increasing in the USA. The rate of biopsy-confirmed HCC increased from 1.3 per 10^5 persons in the period from 1978 to 1980 to 3.0 per 10^5 persons in the period from 1996 to 1998 (7). This increase is 82% after adjusting for changes in age, race, and geographic

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region of origin between the two time period cohorts. Currently, only thyroid cancer is increasing at a faster rate than HCC, and HCC has had the largest increase in death rate of any cancer in the USA (4). The greatest proportional increase of biopsy-proven HCC occurred in the late 1990s. Paradoxically, this is a time when imaging technology became much more sensitive, and biopsy confirmation was no longer required in the majority of tumors. Thus, the reported incidence data certainly underestimate the true incidence. The age-adjusted incidence rate for all reported cases, whether or not there was tissue confirmation, was 4.1 per 10^5 in 1998 to 2000 (7). This increase is driven by the high rate of hepatitis C virus (HCV) infection during the period from 1960 through the mid-1980s. As has been predicted by mathematical models, the increase in HCC has been driven by an increasing proportion of those patients developing cirrhosis over time (8, 9).

The overwhelming majority of HCC cases occur in patients with chronic liver disease (10). Approximately 80% to 90% have cirrhosis, and most of the remainder have moderate to advanced fibrosis. A small proportion of cases have normal histology (no fibrosis) or no apparent cause of liver disease (11, 12). Cirrhosis of any cause can result in HCC (see discussion of risk factors), but chronic viral hepatitis accounts for more than 80% of cases worldwide (2). Among patients with cirrhosis due to hepatitis C, HCC is the first complication to develop in 27% of patients; is the most common complication; and is the main cause of death (44%) (13). The average annual risk of HCC in patients with cirrhosis from HCV is 3.2% (13). The annual risk in Japan is approximately 6% to 7% (14). Among patients without cirrhosis, the annual risk increases as the stage of fibrosis increases (F0 or F1 [none or minimal portal fibrosis] = 0; F2 [periportal fibrosis] = 1.5%; F3 [bridging fibrosis] = 5.1%) (15). In patients with chronic hepatitis B, the yearly risk is 0.02% to 0.2% among inactive HBsAg (hepatitis B surface antigen)–positive patients, 0.1% to 1.0% in persons with chronic hepatitis without cirrhosis, and 2.2% to 3.2% in patients with cirrhosis (16). Loss of detectable virus with antiviral therapy decreases the risk of subsequent HCC but does not eliminate it (17, 18).

In the USA, the average age of diagnosis of HCC is 65 years, and the vast majority of cases occur after age 40 (7). The age has gradually decreased with time, reflecting immigration patterns (hepatitis B birth-acquisition cohorts) and an increased proportion of cases associated with chronic hepatitis C. About half of cases are in whites, 15% in Hispanics, 13% in blacks, and the remainder in other groups, predominantly Asians. These proportions reflect the relative prevalence of hepatitis infections and alcohol use patterns in the groups. There is a wide state-to-state variation in HCC incidence, with the highest age-adjusted rate in Hawaii and the lowest in Iowa and Utah (7). The differences are partly explained by racial, economic, and lifestyle practices. Seventy-four percent of cases occur in men, and male predominance is a worldwide characteristic of this tumor (2). Although this predominance may relate in part to hepatitis prevalence and alcohol use, the major reason for it is unknown. However, a recent report suggested that estrogen may inhibit the ability of proinflammatory cytokines to induce interleukin-6–dependent cell proliferation (19).

Table 1. Causes of hepatocellular carcinoma in the USA (approximate proportions)*

Cause	Percentage
Chronic viral infections	
Hepatitis B	15–17
Hepatitis C	47–55
Hepatitis C + alcohol	27 of above
Both	2–5
Other causes of cirrhosis	
Alcohol	9
Cryptogenic	7
Other†	6
No cirrhosis or virus	4

*From references 7, 22, 27.

†Of 15 patients included under "Other," 4 had hemochromatosis, 3 had alpha-1 antitrypsin deficiency, 3 had primary biliary cirrhosis, 2 had primary sclerosing cholangitis, 2 had autoimmune hepatitis, and 1 had nonalcoholic steatohepatitis (22).

Most patients with HCC will die of their malignancy. The Surveillance Epidemiology and End Results (SEER) database reports that 76% to 95% of patients die as a direct consequence of tumor progression (4). HCC is reported to account for 50% to 70% of liver-related mortality (20, 21). One- and 3-year survival rates were 36% and 17%, respectively, in the SEER registry from 1998 to 2000 (7). This finding represents a small improvement over time and is likely due to the small proportion of patients who receive ablative or surgical treatment. Of the 12% of HCC patients who were resected or transplanted, the 1- and 3-year survival rates were 70% and 55%, respectively (7).

RISK FACTORS

As previously discussed, nearly all HCC occurs in the setting of cirrhosis or advanced fibrosis. Thus, any cause of liver disease that can result in cirrhosis should be considered a potential risk factor for HCC. Not surprisingly, the most common causes of cirrhosis (hepatitis B virus [HBV], HCV, and alcohol) are also the most common causes of HCC *(Table 1)* (22). However, HCC is seen, albeit less commonly, in patients with cirrhosis or fibrosis due to other causes such as genetic hemochromatosis, autoimmune hepatitis, primary sclerosing cholangitis, nonalcoholic fatty liver disease, alpha-1 antitrypsin deficiency, Wilson disease, primary biliary cirrhosis, and certain metabolic liver diseases. The approximate risks by disease are discussed below and listed in *Table 2.*

Chronic viral hepatitis

Hepatitis B. HBV infection is the most common cause of HCC worldwide, accounting for 50% to 55% of all cases. Most cases occur in patients with cirrhosis, but a significant proportion, ranging from 30% to 50%, occur in noncirrhotic patients

Table 2. Estimated annual risk of hepatocellular carcinoma according to etiology of liver disease in the USA*

Etiology	Annual risk
Hepatitis B	
Perinatal acquisition/no cirrhosis	0.1%–0.8%
Cirrhosis	2.2%
Hepatitis C cirrhosis	3.2%–4.2%
Alcoholic cirrhosis	0.3%–1.0%
Hepatitis C + alcohol	See text for discussion
Genetic hemochromatosis/cirrhosis	1.0%
Cryptogenic cirrhosis	1.0%
Nonalcoholic steatohepatitis/cirrhosis	0%–0.8%
Other etiologies of cirrhosis	<1%

*For comparison, the lifetime cumulative risk of HCC in the US general population is 0.42%–0.88%.

(23). Nonetheless, the relative risk of HCC is higher in cirrhotic patients (11.8 vs all other chronic hepatitis B without cirrhosis) (21, 24). The risk appears to be highest in patients with perinatal acquisition of infection (23). Although the latency between infection and HCC is typically decades, some cases may even develop in childhood. The annual incidence has been estimated at 826/100,000 (0.8%) overall and 2768/100,000 (2.76%) for patients over age 35 years (23). Other factors influencing the development of HCC in patients with chronic hepatitis B include gender, degree of viral replication, HCV or delta coinfection, aflatoxin exposure, and alcohol, although the latter is probably related to a more rapid progression of fibrosis (23).

Hepatitis B is one of an increasing number of human viruses, including HBV, HCV, Epstein-Barr virus, Kaposi sarcoma–associated herpesvirus, human papillomavirus, and human T-cell leukemia virus, which have been directly linked to carcinogenesis. The pathogenesis of HCC in patients with chronic HBV infection remains speculative, however, and it is apparent that no single mechanism is predominant. HBV DNA sequences can be integrated into liver tissue, and this likely occurs early during the course of infection (acute hepatitis) (25, 26). Integration in nontumorous tissue is common (more than 70%) and predates development of HCC, thus suggesting that progressive clonal expansion might occur during the course of chronic liver disease. Inflammation results in increased hepatocyte proliferation, which may facilitate rearrangement of integrated viral sequences. Integration may result in host gene deletions, rearrangements, and chromosome transpositions and instability (26). Furthermore, integration can occur in genes encoding cell signaling and proliferation proteins. Some of these targets, such as the telomerase gene, are common, suggesting a common pathway in hepatocarcinogenesis. A significant number of tumor cells demonstrate integration of hepatitis B X (HBx) or truncated envelope (S or preS2) sequences. HBx transactivates a number of cellular promoters and therefore might activate cell signaling pathways that regulate target gene expression and cell proliferation (26). In addition to these HBV-specific pathways, inflammation and cirrhosis per se result in cell proliferation that can lead to gene instability and rearrangements, a mechanism that may be most important in nonviral causes of cirrhosis.

Hepatitis C. Like HBV, HCV is commonly associated with the development of HCC and currently explains about 30% of cases worldwide (2). HCV is the most common cause of HCC in the USA, Europe, and Japan, accounting for 47%–49%, 56%, and 75% of cases, respectively (27, 28). The proportion of HCC caused by HCV increases yearly in the USA and doubled between the mid-1980s and the late 1990s (7). The proportion has tripled in Japan over the last 4 decades (28). In contrast to HBV, almost all HCV-related HCC occurs in the setting of cirrhosis or advanced fibrosis. The average time from onset of HCV infection until development of HCC is about 28 years (29), but the risk increases to 3% to 7% per year after development of cirrhosis *(Table 2)* (30, 31).

The mechanisms of tumor development in patients with chronic hepatitis C are not known. Although often attributed to the inflammatory effects of chronic hepatitis and fibrogenesis alone, this seems unlikely given the high risk compared with other causes of chronic liver disease. Thus, the virus likely plays some role in the process. This concept is supported by the observation that the risk of HCC remains about 2.5-fold higher in cirrhotic patients who fail to clear HCV with antiviral therapy than in those who eradicate infection (32). In contrast to HBV, however, HCV is an RNA virus without reverse transcriptase activity and therefore does not integrate into the host genome. Nonetheless, several viral proteins have properties that make them suspects of interest. In particular, the HCV core protein impacts numerous cellular processes, including apoptosis, cell signaling, transcription activation, cell transformation, and immune response (33), while the E2 envelope protein and the nonstructural NS3 viral protease interfere with the activation of endogenous interferon, which may increase cell proliferation and inhibit host cancer surveillance (34, 35).

Alcohol

According to the Alcohol Epidemiologic Data System of the National Institute on Alcohol Abuse and Alcoholism, 4.8% to 5.9% of adults in the USA are heavy alcohol consumers, and 6.9% are considered to be alcohol dependent (36, 37). (Heavy drinking was defined as having on average >2 drinks per day for men and 1 drink per day for women during the past month.) Regular and heavy alcohol use is cultural in many parts of the world and is especially common in parts of Europe. For example, 36% of patients hospitalized for nonliver reasons in Italy had a history of consuming more than 60 g of alcohol per day (38). If alcohol were a direct hepatic carcinogen, the risk of HCC would be exceedingly high in these heavy alcohol users. However, alcohol appears to be associated with HCC only as a consequence of alcoholic liver disease, in particular cirrhosis. It has been suggested that 10 years' consumption of >80 g of alcohol per day for men and 20 g per day for women is generally required before there is a significant risk of liver disease. Not surprisingly, then, similar consumption is also associated with

the risk of HCC (39). Indeed, cirrhosis is present in almost all cases of HCC in patients with alcoholic liver disease, although rare cases of HCC in patients with alcoholic hepatitis, with or without fibrosis, have been reported (40). In prospectively followed patients with alcoholic cirrhosis, the risk of HCC is 0.3% to 1.0% per year (41, 42), a rate much lower than with viral-associated cirrhosis. Interestingly, the risk of HCC has been reported to be higher in patients who have recently discontinued alcohol than in active drinkers (43). This is probably an artifact related to either discontinuation of alcohol when decompensation occurs or shortened survival in those who continue to drink (42, 43).

Direct data supporting alcohol use per se in the pathogenesis of HCC are lacking and the relationship, if any, is controversial (44, 45). The risk of HCC is highest in patients with heavy alcohol use and cirrhosis due to chronic hepatitis C (46–50). This suggests that perhaps the major impact of alcohol on HCC risk is its effect in accelerating fibrosis progression in patients with chronic hepatitis B and C. Indeed, patients with chronic HCV infection who drink alcohol are far more likely to develop cirrhosis or HCC, and the probability is proportional to alcohol intake (46, 51–54). The relative risk of HCC was much higher when both HCV and heavy alcohol use were present than for either factor alone (66.3 for both vs 23.3 for HCV and 4.6 for alcohol) (55). Furthermore, Niederau reported that the duration of HCV infection and presence of cirrhosis were more important than alcohol use in predicting HCC (54). Nonetheless, habitual or heavy drinkers with chronic hepatitis C develop HCC on average 5 years earlier than patients with no or low alcohol intake (56, 57). The effects of occasional or modest alcohol intake in patients with HCV infection are not known.

Alcohol has long been recognized as a major risk factor for other cancers as well, including cancers of the oropharynx, larynx, esophagus, and possibly breast and colon. The pathogenic mechanisms by which alcohol predisposes to HCC and other cancers in patients with heavy alcohol exposure are not known. It is not known whether alcohol is directly carcinogenic for these tumors or acts as a cocarcinogen. Acetaldehyde, the main metabolite of alcohol, causes hepatocellular injury and is an important factor in causing increased oxidant stress, which damages DNA. Malnutrition associated with alcohol intake is associated with defects in DNA methylation, an essential pathway in gene control (43).

Other chronic liver diseases

Hepatic iron overload is associated with an increased risk of HCC. Patients with genetic hemochromatosis have a risk of HCC that may be increased as much as 200-fold compared with that of the general population (58). The risk is approximately 1% per year in those with cirrhosis (59); however, occasional cases occur in patients without known cirrhosis. Patients with genetic hemochromatosis and cirrhosis have decreased survival that is primarily related to development of HCC (60). Depletion of iron stores by phlebotomy does not decrease the risk of HCC once cirrhosis is established (61). Concurrent alcohol abuse and hepatitis B are both known to further increase the risk of HCC (61). Finally, iron overload from other causes may also increase the risk of HCC (61).

HCC is unusual with other causes of cirrhosis such as Wilson disease, primary biliary cirrhosis, autoimmune hepatitis, and alpha-1 antitrypsin deficiency. The annual risk in patients with cirrhosis from these diseases is probably well below 1% (16).

Between 5% and 30% of cases of HCC do not have an apparent cause of liver disease (cryptogenic). These cases might be explained either by unrecognized viral infection or other liver diseases that remain undiagnosed (including fatty liver disease) or by as yet unrecognized causes of HCC. The former may explain a major proportion of such cases, particularly in areas where hepatitis is endemic. A variable but surprisingly high proportion of HCC cases that are negative for HBsAg and anti-HCV nonetheless have molecular markers of those infections (seronegative viral hepatitis). HBV DNA is present in 8% to 100% (mean, approximately 30%) of cases, and HCV RNA is detectable in 0% to 38% (mean, <5%) (2). Most HBsAg-negative and HBV DNA–positive cases have other serologic markers of HBV infection, e.g., anti-HBc or anti-HBs.

It has been suggested that cryptogenic cirrhosis often represents a late consequence of nonalcoholic steatohepatitis (NASH) since many of these patients have risk factors for NASH (62). Furthermore, a recent review found that type 2 diabetes was associated with an increased risk of HCC (odds ratio, 2.5) irrespective of alcohol use or HCV infection (63, 64). However, the risk of HCC in prospectively followed patients with NASH cirrhosis is low, ranging from 0% to 0.8% per year (16, 65–67). The risk of all liver-related mortality (HCC and cirrhosis) is similar to the risk of cardiovascular death in these patients (66, 67). However, the prevalence of fatty liver disease is increasing, and NASH might account for a growing proportion of HCC cases in the future despite the low risk.

Other risk factors

HCC has been associated with dietary exposure to aflatoxin in regions of the world, including sub-Saharan Africa and Asia, where fungal contamination of grain is common. This risk appears to be confined to patients with chronic HBV infection. HBsAg-positive patients who have detectable aflatoxin-albumin adducts in the urine have a significant increase in HCC risk compared with those who lack this marker (odds ratio, 6.0) (68).

Prolonged exposure to high levels of estrogen oral contraceptives has been associated with hepatic adenomas and HCC (69), but the relationship is controversial and more recent formulations have not been associated with this risk. Cigarette smoking has been independently associated with HCC in several epidemiologic studies from Asia, but this effect, if it truly exists, is minimal.

PATHOGENESIS

The mechanisms by which viruses and/or hepatic fibrosis lead to HCC are not entirely clear. It is, however, clear that two general processes are involved. The first is not specific to a particular etiology but rather involves a wide variety of dysregulated mechanisms that result from hepatic inflammation, necrosis,

and regeneration. Signaling dysregulation that favors tumor growth involves many different factors such as insulin-like growth factors, hepatocyte growth factor, and the Wingless (Wnt)/beta-catenin signaling axis (70, 71). These factors are up-regulated in HCC, but it is difficult to discern the relative contributions of each since their functions and effects often overlap and alterations accumulate over time. As a result, growth may accelerate and signals may become unresponsive to inhibitory factors.

Recently, gene expression profiles of tumors were analyzed in 103 HCV-related HCC (72). Three patterns were associated with pathway activation (Wnt/beta-catenin, tyrosine kinase receptor activation, and interferon response overexpression) while another was associated with overexpression of several proliferative and tumor activation factors associated with chromosome 7 polysomy. Additionally, tumor cells may evade normal apoptosis mechanisms and facilitate angiogenesis (71). Finally, there are also procarcinogenic mechanisms that are specific to a particular etiology.

These mechanisms are more in line with the classical theory of successive cellular gene mutations (multiple hits) as the cause of cancer (73). In the case of hepatitis B, integration of viral DNA into the host genome might lead to chromosomal instability and mutations in normal proliferation regulatory factors, including tumor suppressor genes such as p53 (74). Thus, it would be the cumulative effect of these alterations that would result in HCC. Other cofactors might provide the second hit. For example, aflatoxin exposure may also result in p53 mutations, vinyl chloride causes K-ras mutations, and hepatic adenomas and adenomatosis are associated with hepatocyte nuclear factor 1α mutatations (75). The pattern of these dysregulatory processes is probably responsible for the wide variation in the clinical and histological presentation of this malignancy.

DIAGNOSIS

Alpha-fetoprotein

Alpha-fetoprotein (AFP) is a fetal glycoprotein produced in fetal liver. Its production falls after birth, and its synthesis is repressed in adults. AFP has been used as a serum marker for HCC for decades. In the years prior to sensitive imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), AFP was felt to be both sensitive and specific for HCC. However, it is now apparent that this is not the case. The test has limited specificity, and the presence of chronic inflammatory liver diseases such as hepatitis can raise levels to more than 100 ng/mL. Even more problematic, however, is the limited sensitivity of the assay, in the range of 40% to 60% (76). On the other hand, marked elevation of AFP has prognostic value. Our own experience with 239 pathology-confirmed cases of HCC found that only 21% of cases had an AFP value that exceeded 100 ng/mL (22). Tumors associated with an AFP >100 ng/mL were more likely to be multifocal (>1 tumor; 37%) or diffuse (26%), have vascular invasion (32%), and have a tumor burden exceeding the Milan criteria (single tumor >5 cm or up to three lesions all <3 cm) (60%). Following transplantation, recurrence was noted in 44% and 3-year survival was only 38% (vs 69% in others; $P < 0.0001$).

Other serologic markers

Total AFP consists of three glycoforms that are classified according to their binding affinity to the lectin *Lens culinaris* agglutinin (77). These glycoforms include AFP-L1 (nonbinding), which accounts for AFP elevations from nonmalignant hepatic disease, and AFP-L3 (highly bound), which is the predominant form in HCC patients with elevated AFP. AFP-L3 suffers from the same problems with sensitivity as undifferentiated AFP, but elevations are more specific. As with the undifferentiated protein, high levels of AFP-L3 are associated with advanced tumor (78).

Glypican-3 is a heparin sulfate proteoglycan that interacts with cellular growth factors and is overexpressed in, and may therefore promote the growth of, HCC (79). It is detectable in the serum of 40% to 50% of HCC patients, including a third of those without detectable AFP (80). It is also present in patients with some other tumors, including germ cell tumors and gastric carcinoma.

Des-gamma-carboxy prothrombin (DCP) is a protein that is induced in the absence of vitamin K and is an abnormal by-product from disturbed carboxylation during the formation of thrombin (81). DCP acts as an autologous mitogen for HCC cell lines. It is elevated in 50% to 80% of patients with HCC and does not correlate with AFP elevation. In fact, it appears to be more specific for HCC than AFP and is less often elevated in cirrhotic patients without HCC (81, 82). Thus, the combination of DCP with AFP or AFP-L3 might be even more sensitive and specific (82).

Numerous other genes and proteins that are expressed in patients with HCC might prove useful as clinical markers but are not well studied to date. These include alpha-1-fucosidase, AFP mRNA, gamma glutamyl transferase mRNA, human telomerase reverse transcriptase mRNA, vascular endothelial growth factor, tumor-specific growth factor, and others.

Imaging

Any focal lesion in a patient with cirrhosis should be suspected of being HCC. The ability of abdominal imaging to detect HCC has improved dramatically over the last 2 decades, and the methods described below have generally replaced more invasive procedures (e.g., angiography, exploratory laparotomy, and percutaneous biopsy) as the preferred tools to identify hepatic tumors. Despite this progress, however, ultrasound, CT, and MRI remain variably insensitive for detecting HCC, particularly with tumors <2 cm in diameter (22, 83–86). Furthermore, much of the older radiologic literature overestimated the sensitivity of imaging methods since no correlation with whole organ explant pathology was available (22, 83, 86).

New hardware and software technology that was introduced for CT and MRI in 2000 improved the sensitivity of both modalities. MRI is the most sensitive study and identifies almost 80% of tumors, including 63% of tumors <2 cm (22). CT scanning identifies about 70% and ultrasound about 60% (22). All three imaging methods are quite good at estimating tumor size. On the other hand, none are very accurate in documenting the total number of lesions present; this is likely related to

size, different imaging characteristics of tumors, and location. Most important for the clinician is the fact that the accuracy of any imaging modality is also influenced by local technology, expertise, and practice preference. These factors, as well as local availability of different modalities, must be considered when selecting the optimal test for detecting and staging tumors at a particular center. The typical imaging features of HCC are elaborated in *Table 3.*

Ultrasound. Standard ultrasonography is widely available, relatively inexpensive, and easily performed. Thus, it has become the most commonly utilized imaging modality for detection of hepatic masses. Furthermore, it is able to confidently distinguish some benign lesions such as cysts. On the other hand, its use is limited by body habitus, depth of imaging, and inferiority to other imaging modalities. It is quite insensitive in the cirrhotic liver and detects only about 60% of HCC lesions (95% confidence interval [CI], 44%–76%) and typically has difficulty in distinguishing HCC from other lesions such as regenerative nodules (87). It is particularly poor at detecting small lesions (22, 87). The recent use of contrast-enhancing techniques such as microbubbles significantly enhances sensitivity and specificity by providing assessment of arterial flow characteristics, but this technique is not widely used and requires validation (88).

CT and MRI. CT and MRI rely on examination of tissue characteristics during and after arterial contrast enhancement. Typically, images are obtained during the early arterial phase, the late arterial (portal) phase, and a delayed phase (90–120 seconds postcontrast). HCC demonstrates similar characteristics with both methods *(Table 3)*. In general, HCC variably enhances during the arterial phase and progressively loses enhancement, termed "washdown," during the portal and delayed phases. Although most HCC tumors demonstrate these features, not all show significant enhancement (89). It is difficult to compare these modalities because of the small size of most published studies, technical differences between centers (hardware and software), observer variability, and only occasional availability of organ explants for tumor confirmation. In general, however, it does appear that contrast-enhanced MRI is slightly superior to triple-phase or dynamic CT (86). Because some HCC lesions are detected by only one modality, though, the methods should be considered complementary.

Multiphase CT detects at least 68% of HCC tumors (95% CI, 55%–80%) and is highly specific (93%) (89–92). The importance of multiple phases has been repeatedly demonstrated; therefore, noncontrasted CT scans should not be done when screening for HCC. Besides demonstrating washdown in HCC, an additional advantage of delayed images is that they often clarify the diagnosis of pseudotumor or hemangioma that appears hypervascular if only earlier phases are examined (93). There is no advantage to reducing slice thickness to <5 mm (94). Delayed noncontrast CT scanning 7 to 14 days after hepatic arterial lipiodol infusion has been purported to increase sensitivity but probably adds little to other modalities in most situations (95). The major sensitivity limitation for CT, and all imaging modalities for that matter, is in detection of small tumors, <20 mm (22). In addition, transient hepatic

Table 3. Typical features of hepatocellular carcinoma on imaging studies

Imaging study	Features
Ultrasound	Focal lesion; may be hypo-, hyper-, or isoechoic
Computed tomography	Arterial enhancement with rapid washdown of contrast during portal and delayed phases; may be atypical and not enhance
Magnetic resonance imaging with gadolinium	Arterially enhancing lesion on T2 with contrast washdown
Magnetic resonance imaging with ferumoxide	No or only partial uptake of iron
Positron emission tomography	FDG uptake in <50%; positive lesions usually advanced; must rule out cholangiocarcinoma

FDG indicates fluoro-2-deoxy-D-glucose.

absorption differences are small inconsistent areas of enhancement that do not indicate tumor but can lead to confusion (96). These need to be recognized for what they are in order to avoid unnecessary and potentially invasive evaluation; follow-up imaging may occasionally be required if the diagnosis is in doubt.

Gadolinium-enhanced MRI detects about 81% of HCC tumors (95% CI, 70%–91%) and is specific (85%) (86). Although most clinicians prefer MRI to CT for HCC, this is center dependent. In general, however, MRI is more sensitive and provides more information than CT scanning. However, some lesions not detected by MRI may be found on CT. Thus, both modalities should be used when the index of suspicion for HCC is high, such as when the AFP level is very elevated. As with other imaging methods, the sensitivity of MRI is less for smaller lesions. One study reported 100% sensitivity for lesions >2 cm, 84% for lesions 1–2 cm, and 32% for tumors <1 cm (97). As described with CT scanning above, transient hepatic intensity differences can be confused with small enhancing tumors (98). Follow-up scanning is prudent if there is any question about their identity, but most do not require further investigation.

Finally, MRI imaging with ferumoxide (Feridex) contrast can be helpful in classifying lesions that do not have diagnostic characteristics of tumor on gadolinium MRI. Ferumoxides are superparamagnetic iron oxide crystals that are coated with dextran or carboxydextran (99). These particles are sequestered by phagocytic Kupffer cells in the normal reticuloendothelial system, but they are typically not retained in tumor tissue. Consequently, normal liver tissue appears dark on T2/T2* relaxation while tumors do not. This feature usually makes tumor appear more prominent, but iron uptake can be variable, making the interpretation of the test sometimes difficult (99, 100). It is important to note that Feridex MRI is less sensitive and has a higher false-positive rate for HCC than gadolinium-enhanced MRI scanning, particularly for smaller tumors, and therefore should not be used for screening (101, 102).

Positron emission tomography (PET). Molecular imaging is based upon spatially localized detection of a molecular or cellular event by a selective marker. These methods have been available for hepatic imaging for decades and include the classic technetium 99m (99m Tc) sulfur colloid scans, as well as gallium 67 and 99m Tc imino diacetate acid (IDA) analogue scans. PET scanning is based upon the ability of certain markers to image molecular events that result from the overexpression of a gene that produces a specific messenger RNA (103). ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is the most commonly used marker employed in PET scanning and is capable of detecting a difference in glucose-regulating mechanisms between some tumors and normal tissue. In liver, type 1 glucose transporter is most common in cholangiocarcinoma, while a rate-limiting glycolytic enzyme, hexokinase type II, is more common in HCC (103). While FDG-PET scanning is an excellent tool for cholangiocarcinoma, it is not particularly accurate for detecting HCC, with a reported sensitivity of about 50% (104). Carbon 11-labeled acetate PET may be more sensitive and specific for HCC. FDG-PET positivity of HCC correlates with AFP level, vascular invasion, and poor prognosis. PET-positive tumors are about twice as likely to progress or recur, even among tumors within the Milan criteria (104). Therefore, while not particularly helpful as a screening test, PET scanning might be helpful in evaluating patients with rising AFP levels without tumor detectable by other imaging techniques (105).

Biopsy

The role of biopsy in confirming HCC is controversial (106, 107). While biopsy was often required for definitive diagnosis before the advent of more sensitive and specific imaging tests, it is less often necessary today. In the setting of cirrhosis, a solid and hypervascular lesion that demonstrates late washdown should be considered to be HCC. The major lesion that leads to confusion is a regenerative nodule, and CT or MRI is usually able to distinguish these. Small and/or equivocal lesions can be watched, and the diagnosis will often become evident as tumor characteristics evolve or the lesion grows. Biopsy can be performed if the diagnosis remains in question and the result will influence the treatment plan. In such cases, the result of the biopsy is helpful if it is positive. Negative fine-needle aspirate results should be interpreted with caution. The risk of tumor seeding of the biopsy track is extremely low (108).

SURVEILLANCE STRATEGIES

Surveillance for HCC in patients with cirrhosis or long-standing hepatitis B infection makes sense and has been common practice for many years. The purpose is to identify tumors early when they might be more curable. Thus, the ultimate goal of surveillance is to decrease HCC-related mortality. However, the rationale for screening has been weak until recently, when effective treatment became available, and data supporting the effectiveness of screening remain limited (109).

The most commonly used screening strategy is serum AFP testing and ultrasonography at intervals of 6 or 12 months. This interval is based on the low incidence of HCC in those at risk, typically 1% to 4% per year, and the slow growth of these tumors, with a median estimated doubling time of 117 days (110). The optimal interval and method for screening are not known and may vary depending on the indication for screening. There appears to be no difference in survival for patients screened at 6- or 12-month intervals (111). However, the recent availability of effective treatment (see next section) offers management options that were not previously available, so earlier identification of tumor might now be worthwhile. Shorter screening intervals may occasionally pick up tumors that were missed because of the limited sensitivity of imaging tests (tumor too small to be detected).

Indeed, a large randomized study has recently demonstrated a survival benefit of surveillance. Zhang and colleagues randomized 18,000 Chinese citizens with evidence of current or past HBV infection to surveillance AFP and ultrasound every 6 months or no surveillance (112). Although compliance with the screening regimen was poor (about half), mortality was reduced by 37% in the surveillance group. The Zhang study confirms the earlier observation that unscreened patients who only present when they develop symptoms do very poorly, with 5-year survival of only 0% to 10% (112).

A case might be made for more frequent screening when the goal is ablative management (see next section) or transplantation. Several studies have now shown that surveillance detects tumors while they are smaller and less likely to

Table 4. Groups of patients for whom surveillance is recommended based on the practice guideline from the American Association for the Study of Liver Diseases*

Hepatitis B carriers:
- Asian males ≥40 years
- Asian females ≥50 years
- All cirrhotic hepatitis B carriers
- Family history of HCC
- Africans over age 20

For noncirrhotic hepatitis B carriers not listed above, the risk of HCC varies depending on the severity of the underlying liver disease and current and past hepatic inflammatory activity. Patients with high hepatitis B virus DNA concentrations and those with ongoing hepatic inflammatory activity remain at risk for HCC:
- Non–hepatitis B cirrhosis
- Hepatitis C
- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis

Although the following groups have an increased risk of HCC, no recommendations for or against surveillance can be made because a lack of data precludes an assessment of whether surveillance would be beneficial:
- Alpha-1 antitrypsin deficiency
- Nonalcoholic steatohepatitis
- Autoimmune hepatitis

*From reference 109.
HCC indicates hepatocellular carcinoma.

Table 5. Treatment options for hepatocellular carcinoma

Treatment	Effect
Surgical resection	Potentially curative if within Milan limits
Total hepatectomy/transplantation	Potentially curative if within Milan limits
Local ablation	
Radiofrequency ablation	Potentially curative, particularly if <3 cm
Transarterial chemoembolization	Potentially curative for small lesions; may require multiple sessions
Radiotherapy	
External beam	Ineffective
Modulated or guided irradiation	Typically palliative; may downsize lesion
Yttrium 90 glass microspheres	Typically palliative; may downsize lesion
Systemic therapy	
Chemotherapy	Ineffective
Hormonal therapy	Ineffective
Interferon	Ineffective
Octreotide	Ineffective
Thalidomide	Limited effect
Sorafenib	Limited effect in advanced disease

have extended beyond the point where intervention is likely to make a difference (113–115). We recently found that patients with HCC discovered at the time of liver transplantation had the tumor identified almost 90% of the time if an MRI was performed within 3 months of transplantation, while the number was only 60% to 80% when imaging had been done 6 to 12 months previously (22). Clearly, shorter intervals are also indicated when tumor is suspected, e.g., with a progressively rising AFP level or a suspicious area on a previous imaging study.

The method of imaging to be used in screening depends on several factors. Although triple-phase CT and MRI scanning are most sensitive, they are expensive and typically not practical for routine use. They should, however, be considered when ultrasound either is technically difficult or identifies a suspicious area.

Finally, it is important to remember that surveillance is only likely to be beneficial if applied to those who have an appreciable risk of developing HCC and are amenable to treatment of the tumor. It has been recommended that surveillance be applied when the risk exceeds 1.5% per year (109). The recommended groups for screening are listed in *Table 4* based on the American Association for the Study of Liver Diseases practice guideline (109). The reader is referred to this excellent review for explanations of the groups.

TREATMENT OPTIONS

Many options for treating HCC now exist *(Table 5).* To optimize outcomes, however, these treatments need to be allocated appropriately *(Figure).* Potentially curative therapies such as resection and transplantation should be directed at tumors that have been shown to benefit most from those procedures.

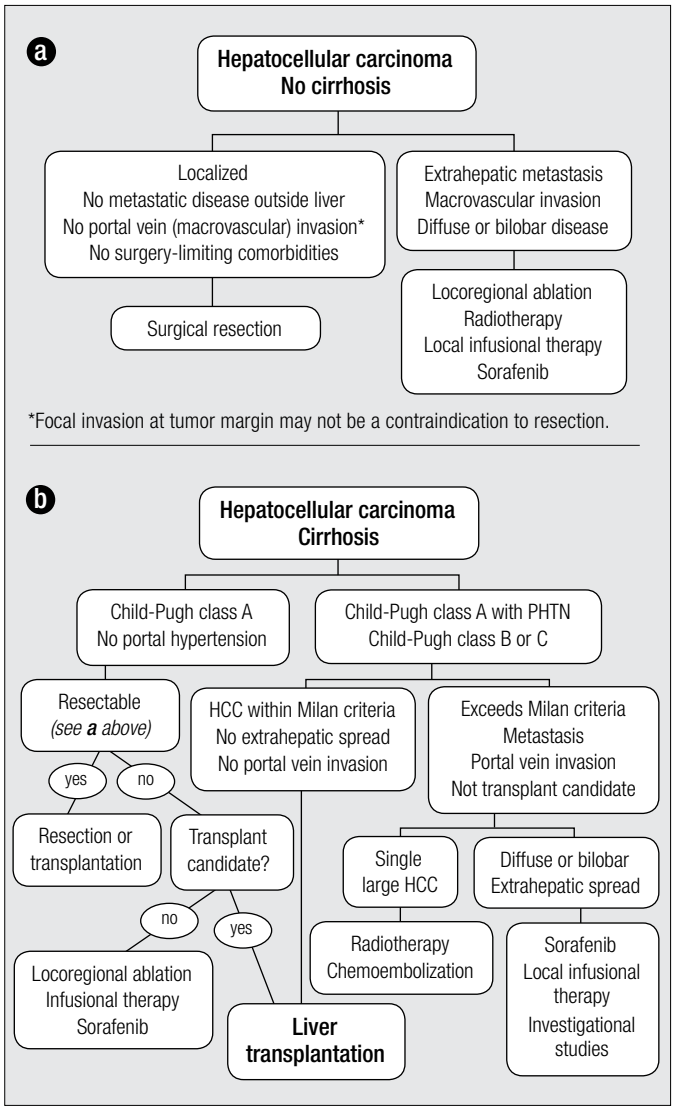

Figure. Algorithm for management of hepatocellular carcinoma (HCC) in patients with **(a)** no cirrhosis or **(b)** cirrhosis. PHTN indicates pulmonary hypertension. See text for description of interventions.

Ablation and palliative procedures should be restricted to patients who have contraindications to resection or transplantation or have tumors that are unlikely to benefit from those procedures. In fact, a recent publication suggested that only 34% of patients with a potentially curable tumor (single lesion <5 cm or multiple lesions <3 cm) received definitive therapy (116). Furthermore, 19% of patients with large or extensive multifocal tumors were subjected to resection or transplantation when those procedures were unlikely to provide benefit. Thus, the purpose of the following discussion is to delineate what therapeutic options are available and who is most likely to benefit from them.

Locoregional ablation

Locoregional ablation refers to a variety of intervention techniques that specifically target a tumor or a tumor and surrounding tissue with a process to directly destroy the tumor. Numerous methods of ablation have been developed. Percutaneous ethanol injection utilizes direct injection of absolute ethanol into the

tumor, resulting in dehydration of cells and protein degradation with coagulative necrosis of the tumor and surrounding tissue. Temperature-based methods, including cryoablation, laser-induced thermal ablation, or microwave thermal ablation, utilize drastic temperature changes to cause cell disruption and necrosis. While these methods have enjoyed popularity at some centers, the most popular methods of locoregional ablation are radiofrequency ablation (RFA) and transarterial chemoembolization (TACE).

Radiofrequency ablation. RFA induces thermal ablation by passing high-frequency alternating current through the tumor utilizing electrodes that are placed within the tumor and surrounding tissue. This technique can be applied percutaneously under ultrasonic guidance or directly during laparoscopy or open laparotomy. Laparoscopic or open approaches are usually favored since they allow better tumor visualization and protection of adjacent tissues. RFA is an attractive method for ablating smaller tumors (<3 cm) (117), although newer electrodes make application to tumors up to 10 cm technically possible in some cases. In general, however, patients with advanced hepatic decompensation, large tumors (3 to 5 cm), or multifocal tumors are poor candidates for RFA.

A recent review of studies using RFA in the treatment of HCC found that the procedure was safe and effective (118). Fever occurred in 20% to 30% of cases, but significant complications such as hepatic infarction; portal vein branch thrombosis; subcapsular, perihepatic, or pleural fluid collections; or burn injury to adjacent tissues occurred in <10%. The effectiveness obviously depends upon the selection of patients, tumor size, experience of the operator, and completeness of the ablation. For small lesions (<3 cm), complete ablation after a single RFA session is about 90% to 100%, but larger tumors often require multiple sessions. Complete tumor necrosis is essential.

When RFA is applied to smaller tumors and complete necrosis is achieved, the 2-year local recurrence-free survival is reported to be 96%, with local recurrence of <6%. This may be about the same as the likelihood of developing a completely new lesion elsewhere in the liver. Obviously, selection is key to achieving such favorable outcomes. Recurrence is higher for larger lesions. Five-year overall survival rates are 40% to 70% and reflect both tumor and liver-related mortality (118, 119). Although there are several small trials comparing RFA with other interventions for HCC, it is difficult to compare these methods because of selection bias, technical proficiencies at study sites, and differing measures of outcomes. Only 16 of 223 studies conducted between 2002 and 2005 were considered to be adequate to compare outcomes of any intervention (119). In the randomized controlled studies comparing RFA with ethanol injection, RFA was associated with lower recurrence and higher 2-year survival (119). Thus, RFA is an effective option in some patients.

Transarterial chemoembolization. Most HCC tumors are highly vascular with a rich arterial blood supply, making segmental hepatic artery embolization an attractive therapeutic option. However, embolization alone provides only partial responses in about half of patients, even though tumor progression and vascular invasion may be delayed (120). Thus, bland embolization has generally been employed only as a palliative option. On the other hand, chemoembolization, which includes local hepatic arterial infusion of doxorubicin, mitomycin, cisplatin, or carboplatin in conjunction with embolization, is far more effective. Five randomized controlled trials including a total of more than 500 patients have been done comparing TACE with conservative management, and two of these demonstrated a modest improvement in survival (121). As with other ablative techniques, selection of patients is critical to ensuring good outcomes. Patients should have good hepatic function since ischemic injury can otherwise lead to acute decompensation and death. The embolization should be as selective as possible in order to limit injury, and multiple procedures are sometimes necessary to treat residual tumor or embolize dual blood supply. The procedure is generally safe, although a postembolic syndrome related to cytokine release from tissue necrosis occurs in about two thirds of patients and is manifested by transient abdominal pain, fever, and ileus.

RFA or TACE is often used while patients are listed for liver transplantation in hopes of preventing tumor progression that might preclude later transplantation. Although this strategy might make some sense and the frequent finding of complete tumor necrosis in the explanted liver would support its practice, no study has shown it to be beneficial in improving survival or reducing tumor recurrence.

Intrahepatic arterial chemotherapy infusion

Unlike other organs, the liver receives a dual blood supply through both the hepatic artery and the portal vein. HCC typically develops its blood supply through angiogenesis fed by the hepatic arterial system. Thus, this feature can be exploited by infusing chemotherapy into the arterial blood flow to the tumor while relatively "sparing" the venous blood flow to the surrounding normal liver. Moreover, considerable therapeutic advantage can be achieved by exposing tumor cells to the full brunt of the chemotherapy before it is diluted as it enters the body's general circulation.

The hepatic artery is accessed via the femoral artery, and the dominant "feeder" artery for the tumor is sought by angiography. The catheter is usually positioned as far toward the tumor as practical to allow access to all feeder vessels while sparing other arterial branches from exposure to the agents. The most commonly used chemotherapeutic agents are doxorubicin, which is usually infused first; carboplatin, which follows over the next few hours; and finally the combination of 5-fluorodeoxyuridine and leucovorin (which potentiates the effects of the 5-fluorodeoxyuridine), which is infused over 3 days.

Infusional therapy is palliative, and tumor response is usually much less than that seen with ablative or chemoablative procedures. Thus, it is often used when other options are not available or the tumor burden prevents therapy directed at one or two specific lesions.

Surgery

Surgical resection of HCC, either partial hepatectomy or total hepatectomy with transplantation, offers the best long-term recurrence-free outcome (60%–70% 5-year survival). Surgery

is the patient's best option for cure and should be the first consideration. As with other procedures, selection of patients is critical to optimizing outcome.

Resection. Partial hepatectomy should be considered in patients who a) have no cirrhosis or well-compensated (Child-Pugh class A) cirrhosis; b) have a limited tumor burden that can be resected without a high risk of hepatic failure; and c) have no evidence of macrovascular invasion or extrahepatic malignancy (122).

Complete radiologic assessment of tumor size, number, and location, as well as the vascular anatomy of the liver should be done by dynamic CT scanning or MRI. Extrahepatic spread should be ruled out by imaging as well. The segmental location of the tumor and the underlying liver disease are critical considerations. For example, a noncirrhotic patient can undergo extensive hepatic resection leaving as few as two segments and recover uneventfully. Patients with cirrhosis, even when well compensated, are less tolerant of hepatic volume loss and are often not able to survive resection of more than two segments. Thus, location of the tumor is critical. Liver volume often returns to near baseline within the first 2 months. Patients who exceed the Milan criteria are generally poor candidates for resection, as they are for transplantation. This guideline relates to tumor factors, particularly microvascular invasion, that predict recurrence. Other poor prognostic signs for resection include bilobar distribution, macrovascular invasion (portal vein thrombosis), and significant elevation of AFP.

Perioperative mortality for hepatic resection is low (<5%) when these guidelines are followed. Furthermore, 5-year survival is generally 50% to 60% (123). Recurrence occurs in more than 50% of patients by 5 years (122), but some of this percentage may represent de novo development of new tumors. Furthermore, other complications of cirrhosis account for some of the postresection mortality.

Although neoadjuvant or adjuvant chemotherapy is often provided to patients who receive hepatic resection in hopes of eradicating micrometastases, it has never been shown to be of benefit. Well-designed studies are needed, particularly with preoperative ablation methods, to determine if such interventions are justified.

Liver transplantation. There are no controlled trials comparing outcomes of hepatic resection and liver transplantation for patients who meet the tumor volume thresholds defined by Mazzaferro, the so-called Milan criteria (124). In some cases with good hepatic function and limited tumor burden, the outcomes would likely be similar. However, most patients with HCC have cirrhosis that would preclude extensive resection. Furthermore, resection would do nothing about the underlying liver disease; therefore, the patients would retain a significant risk for future hepatic failure or new HCC lesions. On the other hand, resection does not entail lifelong immunosuppression and does not usually preclude future transplantation.

The early experience with liver transplantation for HCC was dismal, with recurrence in 30% to 55% of cases and 3- and 5-year survival rates of 15% to 54% and 15% to 48%, respectively (125). However, there were no uniform selection criteria, and many patients had large tumors, macrovascular invasion, or multifocal disease. We now know that such patients do very poorly. The current selection criteria for liver transplantation are based on a study of 48 patients by Mazzaferro and colleagues and limit transplantation to patients with a single tumor <5 cm in diameter or up to three nodules with none >3 cm (124). Furthermore, patients with T2 tumors meeting these criteria are given additional priority for transplantation in order to reduce their chance of developing progressive tumor growth while on the waiting list that might disqualify them from transplantation.

These criteria have served our transplant recipients well: 2- and 5-year survival rates are now 91% and 82%, respectively (126). However, it has recently become apparent that the Milan criteria may be overly restrictive and deny transplantation to some patients who would benefit from it (126, 127). Yao and colleagues as the University of California San Francisco have suggested that patients with either a single tumor <6.5 cm or two to three lesions all <4.5 cm and a cumulative diameter not exceeding 8 cm would do as well as patients meeting the Milan criteria, though there is a suggestion that the rate of tumor recurrence may be greater (126). Onaca studied a group of more than 1200 patients transplanted for HCC and found that those with a single lesion ≤6 cm or two to four tumors with none >5 cm had recurrence-free survival equivalent to that of patients meeting the Milan criteria (127). These expanded criteria are utilized in some parts of the country by agreement between centers sharing donor organs, but they have not yet been generally accepted on a national level.

Recurrence of HCC after liver transplantation is low, and survival is equivalent to that of other transplant recipients. However, an increasing proportion of patients currently transplanted with HCC have HCV infection, and these patients all have reinfection of the graft. Many have progressive liver injury, and this ultimately results in lower posttransplant survival (128).

Other options

Radiotherapy. External beam radiation has historically been of little use for HCC. While tumors generally require upwards of 70 Gy to cause cell destruction, normal liver is quite sensitive to radiation and radiation-induced liver damage occurs at doses of 30 to 35 Gy. Diseased or cirrhotic liver may be even less tolerant of this type of injury. The difficulty with traditional external beam radiation is that the beam delivers a dose of irradiation that damages tissues between the beam source and target, e.g., skin and normal liver. This collateral damage limits the dose that can be delivered. Thus, HCC lesions are reputed to be radiation insensitive, while in fact this is not the case.

Recently, several technological modifications of external beam radiation have allowed delivery of tumoricidal radiation doses (129) and thus opened new options to patients with HCC. Intensity-modulated radiation therapy utilizes numerous pencil beams of irradiation of varying intensity that are delivered in a helical pattern as the machine advances through the target slice by slice. The radiation oncologist calculates the desired radiation for the different parts of the target (tumor) and surrounding tissues, and a computer calculates the optimal way

for the machine to deliver it. An enhancement of this process is image-guided radiation therapy and includes recent commercial setups such as the CyberKnife. The method identifies the target through real-time imaging with CT or ultrasound in order to better focus the radiation during patient movement or breathing. Although markers such as boney structure can be used for targeting, generally fiducial markers are implanted to mark tumor margins. The radiation doses are then calculated with a computer algorithm, and the beams are delivered along three-dimensional rotational axes by a beam mounted on a computer-controlled robotic arm. These targeted methods allow delivery of 50 to 75 Gy of radiation to the tumor with a mean of about 16 Gy to surrounding tissues.

Another way to irradiate HCC is the intra-arterial delivery of a radioisotope. TheraSpheres are nonbiodegradable glass microspheres (diameter 25 μm) with beta-emitting yttrium 90 as a component of the glass (130). Yttrium 90 produces a high tissue dose (>50 Gy) with limited depth penetration (2.5–10 mm). The beads are infused through the hepatic artery branch to the desired target, which can be as precise as an arterial branch that supplies only the tumor. The beads can also treat larger areas by being infused into subsegmental, segmental, or lobar branches of the hepatic artery or into the main hepatic artery itself. The degree of effect and collateral damage obviously relates to the precision of the bead infusion. The half-life of yttrium 90 is 64 hours, so radiation exposure is a consideration if resection or transplantation is considered within 30 to 40 days. Radioembolization has the distinct potential advantage of reducing or stabilizing tumor size. This characteristic offers the potential to "downsize" tumors that exceed transplantation limits at the time of diagnosis to a size that might be more amenable to transplantation.

Finally, proton beam radiotherapy utilizes highly charged subatomic particles that are directed at the tumor (131). Proton beam irradiation differs from x-irradiation in that the radiation is delivered as the protons decelerate during their passage through tissue (end of beam travel) rather than when tissue is first addressed and then decrementally reduces during beam travel. Because of this property, the beam can be focused and repeatedly administered over a series of days, allowing doses of about 75 Gy.

Radiation of HCC results in tissue necrosis and often a reduction in tumor size (129). Complete tumor necrosis is possible. However, it is not yet known whether tumor size reduction changes the biology of large tumors and will reduce the chance of metastasis or make these "downsized" patients appropriate candidates for curative therapies such as transplantation.

Chemotherapy. Standard systemic chemotherapy is typically not effective for HCC. The most active agents in vitro and in vivo (via chemoembolization) are doxorubicin and cisplatin. About 10% of patients appear to have variable and partial tumor response, but neither drug provides a survival advantage (132). Hormonal drugs such as tamoxifen, leuprorelin, and flutamide are ineffective (132). Interferon and octreotide also appear to be ineffective (132). Thalidomide may lead to acute tumor lysis or partial response in a proportion of patients with small tumor burdens (133), but again its effect is quite variable.

Recently sorafenib, an oral multikinase inhibitor with activity against Raf kinase and several receptor tyrosine kinases, including vascular endothelial growth factor receptor 2, has been shown to inhibit liver tumor growth in a mouse model and even cause regression at high doses (134). A phase II study in patients with advanced HCC found partial responses in a small proportion of cases (135), but a recent placebo-controlled phase III study in advanced and inoperable HCC cases demonstrated a 44% (3-month) extension of survival and led to Food and Drug Administration approval (136). The role of sorafenib in less advanced HCC requires investigation.

POTENTIAL OPTIONS FOR THE FUTURE

Hepatocarcinogenesis is a complex multistep process, and it is likely that there are several different events or series of events that can eventuate in HCC. These include inflammatory, regenerative, proliferative, and genetic mechanisms. The events may differ depending on the etiology of the predisposing liver disease, e.g., virus, inflammation, or fibrosis. We are now entering an age of molecular therapies that target specific mechanisms in tumor development. It is likely that new agents will be developed that will specifically target mechanisms of HCC development. Particular areas of interest to hepatologists will be drugs, like gankyrin inhibitors, that either repair or bypass p53 suppressor gene inactivation (137, 138) and agents that influence cell cycle regulatory genes (138).

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